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MATERNAL BLOOD PRESSURE IN RELATION TO LOW BIRTH WEIGHT AND THE EFFECT OF A NUTRITIONAL SUPPLEMENT

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MATERNAL BLOOD PRESSURE IN RELATION TO LOW BIRTH WEIGHT AND THE EFFECT OF A NUTRITIONAL SUPPLEMENT

BY

ALYSSA ABREU

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ABSTRACT

Background: Hypertensive disorders of pregnancy impact over 10% of pregnancies worldwide, while increasing the risk of low birth weight. Research is conflicting on the effect of nutrient supplementation on hypertension during pregnancy. The cutoffs to define hypertension have also recently changed to include a lower systolic blood pressure, and little research has examined the association between the newly proposed blood pressure cutoffs and low birth weight.

Objectives: Our objectives were to 1) evaluate the impact of prenatal lipid-based nutrient supplement consumption on maternal blood pressure; and 2) assess the association between maternal blood pressure during early and late pregnancy with infant birth weight.

Study Design: A total of 1320 pregnant women ≤ 20 weeks gestation in Ghana were randomized to receive daily either: 1) iron and folic acid, 2) multiple micronutrients, or 3) a small-quantity lipid-based nutrient supplement. Gestational age was determined by ultrasound and newborn weight measured at delivery. Blood pressure was measured at enrollment and 36 weeks gestation. The effect of the consumption of a lipid-based nutrient supplement on maternal blood pressure was analyzed using ANOVA and ANCOVA, and associations between maternal hypertension and birth weight were examined by linear and logistic regressions.

Results: Mean (±SD) systolic and diastolic blood pressure at 36 weeks gestation were 110±11 and 63±8 mmHg, respectively. The means for systolic and diastolic blood pressure did not differ by supplementation group, (p-value>0.05). The prevalence of high systolic blood pressure (≥ 130 mmHg) and high diastolic blood pressure (≥ 80

mmHg) at enrollment was 6.6% and 3.6% and there was a significant association between higher diastolic blood pressure and lower birth weight at enrollment (**β** = -0.086, SE = 0.001 ; p = 0.011) in adjusted models. High diastolic blood pressure significantly increased the risk for low birth weight (odds ratio = 2.99, 95% confidence interval 1.04-8.62; p=0.042) in adjusted models. At 36 weeks, the prevalence of high systolic and high diastolic blood pressure was 4.3% and 2.4% and lower birth weight was significantly associated with higher systolic (**β** = -0.074, SE = 0.00 ; p = 0.029) and diastolic (**β** = -0.094, 0.00; p = 0.006) blood pressure. Diastolic blood pressure was significantly associated with an increased risk of low birth weight (OR=4.14, 95% CI=0.020).

Conclusions: Daily consumption of a lipid-based nutrient supplement during pregnancy did not have a significant effect on maternal hypertension compared with iron and folic acid or multiple micronutrients among women in Ghana. Both higher systolic and higher diastolic blood pressure were associated with a lower birth weight, although the association of diastolic blood pressure was larger in magnitude. Due to the high rates of hypertension during pregnancy it is necessary to determine effective strategies for prevention. Maternal hypertension may have implications for newborn birth weight, and future research should determine blood pressure cutoffs specific to pregnant populations that effectively identify pregnancies at risk for newborn low birth weight.

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PREFACE

This thesis follows a manuscript format. The manuscript was prepared following the guidelines for submission to the American Journal of Obstetrics and Gynecology. This manuscript has yet to be submitted for review.

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CHAPTER 1

MANUSCRIPT

Title: Maternal Blood Pressure in Relation to Birth Weight and Consumption of a Lipid-Based Nutrient Supplement

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Condensation: There was no significant effect of consumption of a lipid-based nutrient supplement on hypertension during pregnancy. Maternal hypertension was associated with newborn birth weight.

Short Title: Maternal BP in Relation to Birth Weight and the Effect of a Nutrient Supplement

AJOG at a Glance:

A. Due to recent changes in blood pressure cut-offs, it remains unknown whether prenatal lipid-based nutrient supplements affect blood pressure or whether maternal hypertension is associated with newborn birth weight.
B. Adherence to a nutritional supplement was not associated with blood pressure, and maternal hypertension was associated with birth weight.
C. Both high diastolic and high systolic blood pressure were significantly associated with lower birth weight using the new blood pressure cut-offs.

ABSTRACT

Background: Hypertensive disorders of pregnancy impact over 10% of pregnancies worldwide, while increasing the risk of low birth weight. Research is conflicting on the effect of nutrient supplementation on hypertension during pregnancy. The cutoffs to define hypertension have also recently changed to include a lower systolic blood pressure, and little research has examined the association between the newly proposed blood pressure cutoffs and low birth weight.

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Results: Mean (±SD) systolic and diastolic blood pressure at 36 weeks gestation were 110±11 and 63±8 mmHg, respectively. The means for systolic and diastolic blood pressure did not differ by supplementation group, (p-value>0.05). The prevalence of high systolic blood pressure (≥ 130 mmHg) and high diastolic blood pressure (≥ 80

mmHg) at enrollment was 6.6% and 3.6% and there was a significant association between higher diastolic blood pressure and lower birth weight at enrollment (**β** = -0.086, SE = 0.001 ; p = 0.011) in adjusted models. High diastolic blood pressure significantly increased the risk for low birth weight (odds ratio = 2.99, 95% confidence interval 1.04-8.62; p=0.042) in adjusted models. At 36 weeks, the prevalence of high systolic and high diastolic blood pressure was 4.3% and 2.4% and lower birth weight was significantly associated with higher systolic (**β** = -0.074, SE = 0.00 ; p = 0.029) and diastolic (**β** = -0.094, 0.00; p = 0.006) blood pressure. Diastolic blood pressure was significantly associated with an increased risk of low birth weight (OR=4.14, 95% CI=0.020).

Conclusions: Daily consumption of a lipid-based nutrient supplement during pregnancy did not have a significant effect on maternal hypertension compared with iron and folic acid or multiple micronutrients among women in Ghana. Both higher systolic and higher diastolic blood pressure were associated with a lower birth weight, although the association of diastolic blood pressure was larger in magnitude. Due to the high rates of hypertension during pregnancy it is necessary to determine effective strategies for prevention. Maternal hypertension may have implications for newborn birth weight, and future research should determine blood pressure cutoffs specific to pregnant populations that effectively identify pregnancies at risk for newborn low birth weight.

Keywords: Ghana, low birth weight, maternal blood pressure, nutrient supplements, pregnancy outcomes, prenatal supplementation

INTRODUCTION

During a healthy pregnancy, blood pressure decreases from early to mid-pregnancy, increases in late pregnancy, and then returns to pre-pregnancy levels by delivery.[1] However, during pregnancy blood pressure may not change as expected, but gradually rise and result in hypertension (HTN). HTN is defined as a systolic blood pressure (SBP) $\geq$ 130 mmHg or diastolic blood pressure (DBP) $\geq$ 80 mmHg.[2] The definition was recently updated by the American Heart Association from an SBP $\geq$ 140 mmHg or DBP $\geq$ 80 mmHg due to the increased risk for cardiovascular disease in the general population.[2] It is unclear if the new definition is appropriate for predicting pregnancies at risk of adverse outcomes.

Ghana is a low-middle income country located in western Africa. Based on the previous HTN cutoffs, over 20% of pregnancies in Ghana are impacted by HTN,[3] compared to about 10% worldwide.[4] The disparity may be related to lack of access to adequate health care, a delay in seeking health care, or delayed response to maternal health status at the health care facilities.[5]

Hypertensive disorders of pregnancy have been associated with increased risk for low birth weight (LBW),[6] which is defined as a newborn birth weight of $<$ 2500 grams. LBW is associated with infections[7] and trouble breathing[8] for the infant, as well as increased risk for diabetes and obesity,[9] and intellectual and developmental disabilities.[10]

Nutritional supplements may be an effective strategy to decrease the risk for maternal HTN, especially since anti-hypertensive medication may increase the risk for pregnancy complications.[11, 12] Calcium supplementation daily has been associated with

a decreased risk of maternal HTN, although evidence supports calcium supplementation as only protective against HTN for women with low calcium intake.[13] There is emerging evidence that lipids, specifically essential fatty acids (EFA), may play a role in decreasing placental dysfunction and inflammation, and support increased fetal growth.[14, 15] However, EFAs have been associated with reduced risk of maternal HTN and inflammatory markers only in animal studies. Larger intervention studies in women have not found significant associations between EFA supplementation or intake and maternal HTN.[16] Research on nutrient supplementation including EFAs that may decrease the risk of maternal HTN in human populations is needed.

Our objectives were to 1) evaluate the impact of prenatal lipid-based nutrient supplement (LNS) consumption on maternal blood pressure; and 2) assess the association between maternal HTN during early and late pregnancy and newborn birth weight using the new blood pressure cutoffs.

MATERIALS AND METHODS

Study Design

This is a secondary data analysis of the International Lipid-Based Nutrient Supplements (iLiNS) Project; a randomized controlled trial. The research team recruited pregnant women attending select prenatal clinics in the Eastern region of Ghana, to determine the effects of nutrient supplements during pregnancy and the first eighteen months of the newborn's early childhood. For this analysis, data collected from early pregnancy through birth will be used. LNS is a paste designed to be mixed

with local foods, such as maize, cassava, rice, fish, and leafy vegetables, to increase the nutrient and energy content for enrolled Ghanaian women during pregnancy and lactation. Multiple micronutrient (MMN) and LNS supplements followed formulations for United Nations Micronutrient Preparation (UNIMAP) previously used for prenatal micronutrient supplementation in pilot programs among pregnant women.[17] Nutriset S.A.S. (Malaunay, France) produced the LNS in 20g sachets and Dutch State Mines (DSM) South Africa (Kaiseraugst, Switzerland) produced the capsules of the iron and folic acid (IFA) and MMN supplements. A more detailed description of the study population and methods have previously been described.[18]

The iLiNS study protocol was approved by the institutional review boards at the University of California, Davis; the Noguchi Memorial Institute for Medical Research, University of Ghana; and the Ghana Health Service.

Participants

Eligibility for this study was specific to women attending prenatal clinics in southern Ghana between December 2009 through December 2011, an age of at least 18 years old, and a gestational age of ≤ 20 weeks. Reasons for exclusion included a test result that was HIV positive at baseline, a gestational age > 20 weeks, residence > 20 km outside of southern Ghana, history of peanut or milk allergies, severe illness, or the intention to move within two years. Participants consented to screen for eligibility, and if eligible, fieldworkers collected anthropometrics and baseline lab values.

A randomization scheme was designed by a study statistician. Each woman was randomized into either the IFA, MMN, or LNS group. To ensure blinding, an independent party from the research team color-coded supplement capsules of the IFA

and MMN groups to blind investigators, fieldworkers, and participants. Fieldworkers were not aware of the group allocations, and data analysts were blinded until the completion of preliminary analyses

Procedures

At enrollment, the research group distributed surveys to participants and collected demographic characteristics and lab data. The research group collected lab data again at 36 weeks gestation and newborn anthropometric measurements at delivery.

At enrollment, fieldworkers distributed a two week supply of the assigned supplement along with instructions on consumption methods. At bi-weekly, in-home follow-ups with each participant, data on supplement adherence and morbidity, as well as any remaining supplement were collected. Fieldworkers visited the home or hospital at delivery to collect anthropometric measurements of newborns. For 91% of infants, measurements were recorded within 48hrs of birth. Measurements for 9% of infants were not available after 48hrs, and so measurements were collected between 3-14 days after birth.

Primary Outcomes and Definitions

Our primary outcomes to determine the effect of a nutrition supplement on maternal hypertension are mean SBP and mean DBP at enrollment and 36 weeks gestation. Our primary outcome to determine the association between maternal HTN and birth weight is mean newborn birth weight. High SBP was defined as ≥130 mmHg and high DBP as ≥80 mmHg. Consistent with the iLiNS study, for age- and sex-standardization of blood pressure and weight, the WHO 2006 multi-center growth

standard was used.[19] If the baby was measured within 48 hours, birth weight is reported in grams. If after 48 hours, adjustments for weight following the main iLiNS study were employed.

Statistical Analysis - Effect of LNS on Maternal HTN

In this randomized study design, quantifying the as-treated effect of LNS on maternal hypertension was of primary interest. During the study, IFA and MMN capsules were unintentionally mislabeled, causing 92 participants in the IFA group and 85 participants in the MMN group to receive the incorrect supplement. Therefore, this analysis used the supplement treatment assignment actually received and not the treatment originally assigned. A total of 86 women not-exposed in the LNS group, as well as the mixed-exposure women in the IFA or MMN groups were excluded.

The main iLiNS trail included a total sample size of 1,057 (excluding women pregnant during mixed exposure), where IFA = 349, MMN = 354, and LNS = 354. Our sample size for each group is consistent with the main iLiNS trial and included the total sample size of 1,057. All tests were two-sided, at a 5% level of significance.

Residuals were assessed for normality using a Shapiro-Wilk statistic. Pre-pregnancy body mass index (BMI), C-reactive protein (CRP) at enrollment, and α1-acid glycoprotein (AGP) at enrollment were not normally distributed and were logarithmically transformed for analysis. The heteroscedasticity assumption was also examined through the plots and no outliers were identified through visual identification in histograms or scatterplots.

Variables that were possible confounds and had a statistically significant association with the outcome ($p<0.1$ in univariate models) were included in an

adjusted regression model. To avoid collinearity, variables were considered in the separate logistic regression models to assess the effect of the intervention on maternal blood pressure. If a variable was significantly associated with the effect of the intervention, logistic regression was used to determine if the effect of LNS on blood pressure was significantly different between groups. The null-hypothesis was rejected at the 0.05 level.

Linear regression was used to estimate the study intervention effects on blood pressure. For the continuous outcomes, the difference between the three group means was tested with ANOVA and ANCOVA models. If the null-hypothesis was rejected at the 0.05 level, post-hoc pairwise comparisons across the three intervention groups was tested using the Benjamini-Hochberg procedure to adjust for multiple comparisons.[20]

Due to the number of participants exposed to the incorrect supplement, a sensitivity analysis was conducted to determine if the exclusion of those women influenced the results. The analyses determining the effect of LNS on maternal HTN was repeated with all participants included.

Statistical Analysis - Association Between Maternal HTN and Birth Weight

We evaluated normality of the residuals using a Shapiro-Wilk statistic. The distributions of pre-pregnancy BMI, CRP and AGP at enrollment had deviations from normality, and were logarithmically transformed for analysis. The heteroscedasticity assumption was examined through the residual versus fit plot. A scatterplot between the independent and dependent variables was visually examined to check that the relationship between the predictor and response was linear. No outliers were visually identified through histograms or scatterplots.

The covariates recorded at enrollment that had a statistically significant association with the outcome ($p<0.1$) were included in adjusted regression models. For continuous predictors, collinearity was checked by running models with covariates and an examination of variance inflation factors (VIF). VIF above 10 was considered problematic, however, there were no variables that exceeded a VIF of two. Therefore, there was no evidence of collinearity and all variables significantly associated with the outcome were included in adjusted models.

Continuous variables were analyzed with linear regression if they were determined to have a statistically significant association with the outcome. Multiple linear regression models were used to determine the association between systolic and diastolic blood pressure and birth weight.

RESULTS

The total sample size used in this analysis included 1,057 pregnant women, with a 19% loss to follow up. There were 349 women included in the IFA group, 354 in MMN and 354 included in the LNS group. Means ($\pm SD$) and percentages of maternal characteristics at enrollment for the IFA, MMN and LNS groups are shown in Table 2, as well as the geometric mean and 95% confidence interval (CI) for CRP and AGP. The prevalence of HTN at 36 weeks gestation was 5.3% (SBP ≥ 130 mmHg or DBP ≥ 80 mmHg). The prevalence of high SBP at 36 weeks gestation was 4.3% and high DBP was 2.4%.

Supplement Group Comparisons

Table 3 shows the mean SBP and DBP at 36 weeks gestation by supplement group. The unadjusted and adjusted means of SBP and DBP at 36 weeks gestation

were not significantly different between groups ($p>0.05$). Maternal age modified the effect of the intervention on maternal SBP at 36 weeks; $F(2, 1054) = 3.40$, (p-value for interaction = 0.034). Maternal age was categorized into high and low age groups using the median, and the effect of the intervention on maternal SBP at 36 weeks was no longer significant, $F(2,1054) = 1.40$, (p-interaction = 0.246). There were no significant differences in risk for maternal HTN between IFA or MMN and LNS (table 4).

In the sensitivity analysis including all women (exposed and not exposed) neither SBP or DBP means significantly differed by supplementation group in unadjusted or adjusted analysis.

Maternal BP and Newborn Birth Weight.

Table 5 presents the characteristics of total, normal, and HTN groups at enrollment. Women with HTN had a significantly higher age, pre-pregnancy BMI, height, SBP and DBP compared to those with normal blood pressure; ($p<0.05$).

At enrollment, SBP was not significantly associated with a lower birth weight in unadjusted or adjusted models determining standardized beta (**β**) coefficients (table 6). Similarly, high SBP did not significantly increase the risk for LBW (Table 7). However, as opposed to SBP, DBP at enrollment was significantly associated with a lower birth weight in adjusted models and remained significant after the Benjamini-Hochberg procedure (**β** = -0.086, SE = 0.001 ; p = 0.011). High DBP at enrollment significantly increased the risk for LBW (odds ratio (OR) = 2.99, 95% confidence interval (95% CI)= 1.04-8.62; p=0.042) when adjusting for pre-pregnancy BMI, maternal age, height, assets index, parity, hemoglobin, offspring sex, and treatment

group, SBP and DBP at enrollment. However, after the Benjamini-Hochberg Procedure it was no longer statistically significant (p=0.064).

Unlike early pregnancy, at 36 weeks gestation, higher SBP was significantly associated with a lower birth weight in adjusted models (**β** = -0.074, SE = 0.00 ; p = 0.029). High SBP did not significantly decrease the risk for LBW (OR=2.19, 95% CI =0.72-6.73; p=0.170). Higher DBP was significantly associated with a lower infant birth weight (**β** = -0.094, SE = 0.00 ; p = 0.006) and increased the risk of LBW to over four times the risk of those with normal blood pressure (OR=4.14, 95% CI=0.020).

DISCUSSION

In this study, higher DBP presented a strong association with lower newborn birth weight at enrollment and 36 weeks gestation. SBP was only significantly associated with a lower birth weight at 36 weeks gestation, and only DBP significantly decreased the risk for LBW. LNS did not significantly decrease the risk for maternal hypertension compared to IFA or MMN.

The association between higher DBP and a lower birth weight, and LNS not significantly decreasing maternal blood pressure is consistent with previous research using the previous blood pressure cutoffs. In a study by Bakker et al. (2011), higher DBP had stronger associations with a lower birth weight compared to SBP, as well as an increased risk for LBW.[21] A randomized control trial conducted in Bangladesh found no significant associations between LNS and maternal blood pressure.[22]

Our findings that HTN is associated with LBW may be explained by maternal HTN leading to reduced placental perfusion,[23] placental dysfunction, and increased inflammation.[14] Inflammation may lead to fetal hypoxia that may inhibit fetal growth,

and thereby reduce newborn birth weight.[24] Alternatively, maternal HTN may actually be a consequence of fetal growth restriction, as fetal growth restriction and placental dysfunction may decrease placental vasodilators, which are increasingly important during late pregnancy for blood pressure maintenance.[25] The underlying mechanisms for how maternal blood pressure and birth weight are related remains unclear.

The functional differences between DBP and SBP may explain our findings that DBP and SBP presented different associations with lower birth weight. DBP is largely responsible for cardiac output [26] and the amount of blood flow that the placenta and ultimately fetus may have access to.[25] With increased DBP, there is decreased cardiac output, leading to decreased blood flow to the placenta, resulting in less fetal access to oxygen and nutrients required for growth.[26]

There are strengths and limitations of this study. Limitations to note include missing information related to the use of anti-hypertensive medications, which may affect newborn birth weight. However, we were able to control for all women with a history of HTN prior to pregnancy, which would include those with a history of taking anti-hypertensive medication. That analysis examined women as a cohort, therefore, we are unable to attribute the causation of LBW to maternal HTN. This study also has many strengths including a low loss to follow-up and the reliability of methods. Specifically, ultrasound scans were used to determine gestational age, and both blood pressure measurements and newborn birth weight were measured by trained fieldworkers.

Due to the high rates of HTN during pregnancy and considering the health disparities that exist in developing countries, it is necessary to determine effective

strategies for prevention. Research determining the effect of essential fatty acid supplementation on maternal HTN in human populations is needed. Maternal HTN may have implications for newborn birth weight, and future research should determine blood pressure cutoffs specific to pregnant populations that effectively identify pregnancies at risk for newborn LBW.

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TABLES

Table 1: Composition of supplements given to pregnant Ghanaian women recruited between 2009-2011 in the International Lipid-Based Nutrient Supplements (iLiNS) Project Study.

Nutrient	**IFA**	**MMN**	**LNS**
Ration, g/d		1 tablet	20
Total Energy, kcal		0	118
Protein, g		0	2.6
Fat, g		0	10
Linoleic acid, g		0	4.59
a-Linolenic acid, g		0	0.59
Vitamin A, **µg RE**		800	800
Vitamin C, mg		100	100
Vitamin B-1, mg		2.8	2.8
Vitamin B-2, mg		2.8	2.8
Niacin, mg		36	36
Folic acid, **µg**	400	400	400
Pantothenic acid, mg		7	7
Vitamin V-6, mg		3.8	3.8
Vitamin B-12, **µg**		5.2	5.2
Vitamin D, IU		400	400
Vitamin E, mg		20	20
Vitamin K, **µg**		45	45
Iron, mg	60	20	20
Zinc, mg		30	30
Copper, mg		4	4
Calcium, mg		0	280
Phosphorus, mg		0	190
Potassium, mg		0	200
Magnesium, mg		0	65
Selenium, **µg**		130	130
Iodine, **µg**		250	250
Manganese, mg		2.6	2.6

Iron and folic acid (IFA capsule is standard practice and follows WHO and Ghana Health Service recommendation; multiple micronutrient supplement (MMN) capsule; lipid-based nutrient supplement (LNS) for pregnant and lactating women

Table 2: Characteristics at enrollment of pregnant Ghanaian women enrolled in the International Lipid-Based Nutrient Supplements (iLiNS) Project Study.

		Mean (SD) or %	
Characteristic	*IFA, n=349*	*MMN, n=354*	*LNS, n=354*
Maternal Age	26.5 (5)	26.9 (6)	26.5 (5)
Gestational Age	16.3 (3)	16.2 (3)	16.22 (3)
Parity			
Parous	62%	69%	64%
BMI	24.5 (4)	24.4 (4)	24.7 (4)
Height, cm	158.5 (6)	159.1 (6)	159.0 (5)
Education, completed years	7.6 (4)	7.5 (4)	7.7 (4)
Married or Cohabitating	92%	94%	93%
Offspring Sex			
Female	49%	51%	49%
*CRP**	3.8 (3.3-4.3)	3.13 (2.78-3.52)	3.32 (2.92-3.79)
*AGP**	0.6 (0.6-0.7)	0.6 (0.6-0.6)	0.6 (0.6-0.6)
Mean SBP	112 (10)	111 (12)	112 (11)
Mean DBP	63 (7)	64 (8)	64.33 (8)
Positive Malaria test	9%	8%	11%

*Geometric mean and 95% Cl presented

Abbreviations: IFA, iron and folic acid: capsule is standard practice and follows WHO and Ghana Health Service recommendation; MMN, multiple micronutrient supplement capsule; LNS, lipid-based nutrient supplement for pregnant and lactating women; BMI, body mass index; CRP, C-reactive protein; AGP, α1-acid glycoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3: Mean systolic and diastolic blood pressure at 36 weeks gestation by supplement group in pregnant Ghanaian women of International Lipid-Based Nutrient Supplements (iLiNS) Project Study

	IFA *n=349* *Mean (95%CI)*	***MMN*** *n=354* *Mean (95% CI)*	***LNS*** *n=354* *Mean (95% CI)*	*p*
Unadjusted SBP	109.9 (108.9-111.0)	109.5 (108.3-110.7)	110.2 (109.0-111.4)	0.704
Adjusted SBP	109.9 (108.9-111.0)	109.6 (108.4-110.8)	110.3 (109.1-111.5)	0.958
Unadjusted DBP	62.8 (62.0-63.6)	62.2 (61.4-63.0)	63.1 (62.3-63.9)	0.266
Adjusted DBP	62.8 (62.0-63.6)	62.3 (61.4-63.0)	63.1 (62.3-63.9)	0.668

Abbreviations: IFA, iron and folic acid: capsule is standard practice and follows WHO and Ghana Health Service recommendation; MMN, multiple micronutrient supplement capsule; LNS, lipid-based nutrient supplement for pregnant and lactating women; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Adjusted models included pre-pregnancy BMI, gestational age, maternal age, completed years of education, asset index, food insecurity index, hemoglobin status, maternal height, CRP, AGP, parity, history of hypertension, and malaria status; all covariates were ascertained at study enrollment.

Table 4: Adjusted odds of high systolic or diastolic blood pressure at 36 weeks gestation by supplement group in pregnant Ghanaian women of International Lipid-Based Nutrient Supplements (iLiNS) Project Study

	IFA vs LNS		MMN vs LNS	
	OR	**95% CI**	**OR**	**95% CI**
Normal BP	1.00	-	1.00	-
High SBP (n=45)	0.63	0.27-1.47	0.87	0.40-1.91
High DBP (n=25)	0.56	0.19-1.67	0.93	0.33-2.61

Abbreviations: IFA, iron and folic acid: capsule is standard practice and follows WHO and Ghana Health Service recommendation; MMN, multiple micronutrient supplement capsule; LNS, lipid-based nutrient supplement for pregnant and lactating women; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Adjusted models included pre-pregnancy BMI, gestational age, maternal age, completed years of education, asset index, food insecurity index, hemoglobin status, maternal height, CRP, AGP, parity, history of hypertension, and malaria status; all covariates were ascertained at study enrollment.

Table 5: Characteristics of total, normal, and high blood pressure groups at enrollment of pregnant Ghanaian women of the International Lipid-Based Nutrient Supplements (iLiNS) Project Study.

Characteristic	***Total*** *(n=1057)* ***Mean (SD) or %***	***Normal BP Group*** *(n=1001)* ***Mean (SD) or %***	***HTN Group*** *(n=56)* ***Mean (SD) or %***	***p***
Maternal Age	26.7 (5)	26.6 (5)	28.6 (6)	0.007
Gestational Age	16.2 (3)	16.2 (3)	16.3 (3)	0.857
Parity				0.190
Parous	65%	65%	73%	
BMI	24.5 (4)	24.3 (4)	28.6 (6)	<0.001
Height	158.9 (6)	158.8 (6)	160.5 (6)	0.023
Education, completed years	7.6 (3)	7.6 (4)	7.7 (4)	0.833
Married or cohabitating	93%	93%	93%	0.989
Offspring Sex				0.496
Female	50%	50%	45%	
CRP	3.39 (3.2-3.7)	3.36 (3.1-3.6)	4.75 (3.4-6.6)	0.092
AGP	0.6 (0.6-0.6)	0.6 (0.6-0.6)	0.7 (0.6-0.7)	0.089
SBP	112 (11)	110 (10)	135 (9)	<0.001
DBP	64 (8)	63 (7)	80 (8)	<0.001
Positive Malaria test	10%	10%	10%	0.782

*Geometric mean and 95% Cl presented

Abbreviations: BMI, body mass index; CRP, C-reactive protein; AGP, α1-acid glycoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; HTN, hypertension- SBP ≥ 130 mmHg or DBP ≥ 80 mmHg

Table 6: Unadjusted and adjusted beta (**β**) coefficients of systolic and diastolic blood pressure predictors at enrollment and 36 weeks gestation and newborn birth weight in the International Lipid-Based Nutrient Supplements (iLiNS) Project Study.

	Birth Weight, g **β** (SE)	
	Unadjusted	***Adjusted***
BP at Enrollment		
SBP (mmHg)	0.056 (0.001)	-0.062 (0.001)
p	0.087	0.066
DBP (mmHg)	0.039 (0.001)	-0.086 (0.001)
p	0.230	0.011*
BP at 36wks		
SBP (mmHg)	0.054 (0.001)	-0.074 (0.001)
p	0.101	0.029*
DBP (mmHg)	0.043 (0.001)	-0.094 (0.001)
p	0.192	0.006*

*significant after Benjamini-Hochberg procedure

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure. p = p-value at 0.05 significance level.
Adjusted models included pre-pregnancy BMI, maternal age, asset index, parity, hemoglobin status, offspring sex, maternal height, and treatment group; all covariates were ascertained at study enrollment.

Table 7. Adjusted odds of low birth weight (LBW) predicted by maternal blood pressure (BP) at enrollment an 36 weeks gestation in the International Lipid-Based Nutrient Supplements (iLiNS) Project Study

		LBW (n=93)	
	OR	**95% CI**	***p***
BP at Enrollment			
Normal BP (n=987)	1.00	-	-
High SBP (n=70)	1.04	0.35-3.06	0.948
High DBP (n=38)	2.99	1.04-8.62	0.042†
BP at 36wks			
Normal BP (n=1012)	1.00	-	-
High SBP (n=45)	2.19	0.72-6.73	0.170
High DBP (n=25)	4.14	1.26-13.62	0.020*

*significant after Benjamini-Hochberg procedure
†not significant after Benjamini-Hochberg procedure

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; normal SBP < 130mmHg; high SBP ≥ 130 mmHg; normal DBP < 80mmHg; high DBP ≥ 80 mmHg; LBW, low birth weight – infant born < 2500 grams.
Adjusted models included pre-pregnancy BMI, maternal age, asset index, parity, hemoglobin status, offspring sex, maternal height, and treatment group; all recorded at enrollment.

CHAPTER 2

REVIEW OF LITERATURE

Introduction

Over 10% of pregnancies are impacted by high blood pressure (HTN)[1] which is currently defined as systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 80 mmHg.[2] Maternal HTN is associated with adverse pregnancy and birth outcomes, including increased risk for chronic disease and an infant born with a low birth weight (LBW). [3] To reduce the prevalence of HTN in pregnant populations, current nutrient recommendations are limited to an increase of dietary calcium to one gram daily, with conflicting evidence related to the effect of supplementing additional nutrients to decrease maternal blood pressure.[4]

There are various disorders during pregnancy related to high blood pressure, including preeclampsia (PE), gestational hypertension (GH), and chronic hypertension. PE is a hypertensive disorder of pregnancy that includes proteinuria, in a previously normotensive woman.[5] GH is an SBP ≥ 130 mmHg or DBP ≥ 80 mmHg recorded on two separate occasions during pregnancy or after 20 weeks gestation. Chronic hypertension is diagnosed prior to pregnancy or before 20 weeks gestation.

Maternal Blood Pressure

Blood pressure fluctuations during pregnancy are normal and expected.[6] On average, in normal pregnancies, SBP decreases to 112 mmHg, and DBP decreases to 65 mmHg by 12 weeks gestation.[6] By late pregnancy, around 37 weeks gestation, both SBP and DBP increase to 116 and 70 mmHg.[6,7] These fluctuations in blood pressure result from the blood supply requirements for normal development of the fetus,[8,9] as

well as hormonal influences on vascular remodeling .[10,11] However, there are many risk factors for maternal HTN. Among others, risk factors for maternal HTN include maternal age,[12] chronic hypertension and a history of preeclampsia.[13]

Maternal HTN is associated with complications during pregnancy as well an increased risk for long-term chronic disease. The overall risk for maternal mortality increases, as well as an increase in risk for maternal morbidity; specifically, the risks for cardiovascular disease, kidney disease, diabetes and chronic hypertension is increased.[14-18] Maternal HTN significantly increases the risk (or hazard) by 44% to 300% for ischemic heart disease, myocardial infarcts, myocardial infarct death, heart failure, ischemic stroke, kidney disease, and diabetes mellitus.[14] Although maternal HTN factors may be related to pre-pregnancy cardiovascular risk factors,[19] there are significant associations between hypertensive disorders of pregnancy and cardiovascular risk factors, including a greater BMI, higher SBP and DBP, and elevated levels of insulin and triglycerides.[20]

A strategy to decrease maternal HTN includes the use of antihypertensive medication, although it is recommended that antihypertensive medication should only be prescribed with an SBP $\geq$ 160 mmHg or DBP $\geq$ 110 mmHg due to increased risk for pregnancy complications.[21,22] This is in part due to the fact that all drugs for the treatment of high blood pressure during pregnancy cross the placenta.[23] The consequences of this may include uteroplacental perfusion and maternal hepatotoxicity.[24] The American Heart Association also specifically discourages the use of angiotensin-converting–enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) due to their association with adverse fetal and birth outcomes.[25-27]

However, despite recommendations, antihypertensive medication is increasingly being relied upon during pregnancy.[28] For instance, in a review of antihypertensive medication use during pregnancy in a Medicaid population, the overall use increased almost 50% within six years, resulting in nearly 5% of pregnancies ultimately exposed to antihypertensive medication. Furthermore, participants were unlikely to switch to recommended antihypertensive medications, and continued with medications associated with increased risk for adverse outcomes.[28]

The prevalence and impact of high maternal blood pressure may impact developing countries to a greater degree than developed countries. To be specific, in Ghana, over 19% of pregnancy-related deaths are related to hypertensive disorders of pregnancy,[29] compared to the 7.4% in the United States.[30] The disparity may be related to lack of access to or a delay in seeking health care, or delayed response to maternal health status at the health care facilities.[31] In developing countries, there may also be limited ability to screen for hypertensive disorders, specifically in rural settings.[32] Additionally, in Ghana it is estimated that nearly 43% of Ghanaian adults are obese, with an estimated 27.8% of women being overweight and 21.9% obese.[33] With this in mind, a cohort study conducted in Ghana by Amoakoh-Coleman et al. (2017),[34] determined that women who were obese had three times the risk of gestational hypertension compared to pregnant women with a normal BMI (RR 3.01, 95% CI: 1.06 – 8.52; p=0.04). However, this study had many limitations in that weight was not based on pre-pregnancy weight, but was measured at 20 weeks gestation. Another limitation was that women were excluded from the study if they were

previously diagnosed with hypertension at baseline; this may result in an underestimation of the risk of gestational hypertension.

The underlying mechanisms for causes of maternal HTN remains unclear; however, hypertensive disorders of pregnancy may result from reduced uterine perfusion, placental dysfunction, genetic polymorphisms, and immune maladaptation,[35] as well as their relationship with endothelial dysfunction. In animal studies, there is also evidence that a reduction of uterine perfusion pressure influences the distribution of a peptide receptor produced by the vascular endothelium, endothelin receptor type-B, which decreases vasodilatation and enhances vasoconstriction.[36] Decreases in vasodilatation and enhanced vasoconstriction will increase the arterial pressure through increased arterial resistance resulting in an increased blood pressure. For PE specifically, abnormal uteroplacental blood circulation may lead to maternal endothelial dysfunction, ultimately resulting in maternal HTN and proteinuria.[37] In addition, increased inflammatory markers including C-reactive protein, tumor necrosis factor-α and interleukin-6 may also been associated with hypertensive disorders in pregnancy.[38]

Nutrients and Maternal Blood Pressure

As a whole, research determining the various independent causes of hypertensive disorders of pregnancy are not totally understood, and as such, the relationship between specific nutrient levels or intakes and maternal blood pressure remains uncertain. This is highlighted in a prospective observational cohort study by Oken et al. (2007),[39] which examined the associations between gestational hypertension and, among others, calcium, omega-3 fatty acids, magnesium, folate, and vitamins C, D,

and E. Pregnant women included in the study were participants in Project Viva, with a final sample size of 1718 women. Women completed questionnaires and interviews to collect information related to maternal characteristics and dietary patterns. The study determined that compared with women maintaining a normal blood pressure throughout pregnancy, women with PE had a lower consumption of omega-3 fatty acids, vitamin C, E, folate, and magnesium, while women with gestational hypertension maintained higher dietary intakes of vitamins C, D, and E. However, the risk for PE or gestational hypertension was not reduced, despite intake levels of calcium or vitamin D. Furthermore, women only had a lower risk of PE with increased levels of omega-3 fatty acids and magnesium. That study is just one example of how specific nutrients may have independent associations with hypertensive disorders of pregnancy; and often, the relationships are not as expected.

Calcium

One of the first descriptions of the relationship between calcium and high blood pressure in pregnancy was due to the observation that pregnant, Guatemalan women who were considered poor, had a low prevalence of eclampsia (0.4%) compared to other developing countries (e.g. 12%, India), as well as developed countries (e.g. Japan, 15%).[40] That population also maintained high levels of calcium consumption (1320 mg/day in urban settings) compared to the other countries (347 mg/day, India; 368 mg/day, Japan). A staple food in the Guatemalan diet that contributed high amounts of calcium was maize tortillas, which were cooked and soaked in lime water (calcium hydroxide). Similarly, in Ethiopia, a diet consisting of the grain, teff, and

lime in meal preparation allowed for a daily consumption of ~1075 mg of calcium per day. Meanwhile, the prevalence of eclampsia in Ethiopia was 0.9%.[40]

As research has progressed, calcium supplementation during pregnancy in populations with inadequate calcium levels[41] has been associated with a lower risk for pregnancy complications such as maternal HTN, and adverse birth outcomes. A suggested mechanism is derived from the association between increased calcium intake and decreased parathyroid hormone (PTH). PTH plays a central role in calcium homeostasis and blood pressure regulation. Low levels of calcium signal the parathyroid glands to increase circulating PTH. Increased PTH increases vasoconstriction, which ultimately raises blood pressure and signals the kidneys to increase calcium reabsorption and phosphate excretion; as well as the stimulation of bone resorption to increase calcium levels.[42,43]

Additional mechanisms to describe the relationship between calcium and maternal blood pressure may include the regulation of hormones in addition to PTH, such as calcitriol, a derivative of vitamin D, and calcitonin. High extracellular calcium stimulates the release of calcitonin,[44] which is a hormone produced in the thyroid gland that opposes PTH and can function to increase vasodilation. Therefore, calcitonin has an inverse relationship with blood pressure. Calcitonin gene-related peptide (CGRP) is a member of the calcitonin family,[45] and levels of CGRP significantly increase throughout pregnancy, before returning to pre-pregnancy levels post-delivery.[46]This is consistent with the inverse trajectory of maternal blood pressure in healthy individuals, which decreases until mid-pregnancy and returns to normal near delivery.[6,7] Moreover, in a case-control study with pre-eclamptic women and

matched normotensive women, CGRP was significantly lower in women with pre-eclampsia than controls between 21-29 weeks gestation ($p<0.001$).[47] Hence, it is suggested that increased extracellular calcium, which stimulates calcitonin, results in vasodilation and decreased blood pressure. The reverse may also be true, in that decreased calcium and lower calcitonin levels allows for vasoconstriction and increased maternal blood pressure.

Currently, it is recommended that pregnant women with low calcium intake supplement 1.5-2.0 grams of calcium daily, to decrease risk of HTN.[3] However, while calcium supplementation during pregnancy in populations with inadequate calcium levels has been associated with a lower risk for maternal HTN,[48] it remains uncertain whether calcium supplementation may benefit women with adequate calcium intake.[49]

Vitamin D

Vitamin D is a fat-soluble vitamin, which can be present in the body in inactive form (cholecalciferol). With UVB exposure through sunlight, inactive vitamin D can be metabolized by the liver to calcidiol and converted by the kidneys to the active form, calcitriol[50] . In addition to endogenous sources, active vitamin D can be obtained through nutrient supplements and dietary sources such as fish, mushrooms, and fortified food products[51] . For health promotion and disease prevention, adequate levels of vitamin D for the general population are currently considered to be a concentration of 75 nmol/L, while inadequate levels are < 50 nmol/L.[52] In the United States, it is estimated that > 30% of pregnant women maintain inadequate levels of vitamin D,[53] whereas only 1% of pregnant women in Tanzania are inadequate[54] and 96% in India.[55]

Research related to vitamin D that is of high quality and relatively reliable remains limited, specifically within pregnant populations.[56,57] Therefore, adequate intakes and corresponding health impacts remain unclear.[57] The consequences of a deficiency of vitamin D may include an infant born with low birth weight, an infant born small for gestational age,[58] myopathy (muscle disease),[59] and certain autoimmune diseases; although the extent to which vitamin D impacts diseases independent of calcium requires additional research[60]. During pregnancy, vitamin D has also been associated with a decreased risk for maternal high blood pressure[56] and involvement in calcium maintenance homeostasis.[61]

Research is conflicting on mechanisms by which vitamin D may influence maternal blood pressure.[62,63] One mechanism includes the ability of vitamin D to stimulate calcium absorption, transport and removal across intestinal cells,[64] though recent research indicates an inverse relationship between vitamin D and PTH.[63] As previously mentioned, PTH plays a central role in the calcium metabolic pathway and blood pressure regulation, and decreased levels of vitamin D may increase PTH, thereby increasing vasoconstriction. In a cross-sectional study by Garcia et al. (2013),[62] significant correlations in adjusted models were found between PTH and SBP ($r = 0.146$; $P = 0.010$) and DBP ($r = 0.126$; $P = 0.026$) and PTH and vitamin D status ($r = -0.133$; $P = 0.019$). However, associations between vitamin D status and blood pressure were insignificant. Similarly, Hemmingway et al. (2018), found that PTH decreased significantly in pregnant women with increasing vitamin D, ($P < 0.001$), however there were no significant associations between elevated PTH and

gestational hypertension or vitamin D deficiency and risk of gestational hypertension.[65]

Sodium and Potassium

The American Heart Association recommends the restriction of sodium (Na) to < 1500 mg in the general population, and 2300 mg as the upper intake level to prevent adverse health outcomes.[66] This is because high sodium intake has been associated with an increased risk for high blood pressure and cardiovascular disease in the general population.[67-69]

One suggested mechanism linking sodium intake and increased blood pressure is related to the regulation of extracellular fluid volume. In healthy adults, a renal arterial pressure may signal the kidneys to either retain or excrete sodium in order to control BP, called pressure natriuresis. However, with high sodium intake, the function of hormones in the renin-angiotensin aldosterone system responding to sodium levels and blood pressure may be impaired and result in dysregulation of the extracellular fluid volume and concurrently vasoconstriction.[70] Increased extracellular fluid volume and vasoconstriction may result in increased blood pressure.[71]

One strategy that promotes a restriction of sodium is the dietary approaches to reduce hypertension (DASH) diet, which promotes increased fruits, vegetables, whole grains and the reduction of saturated fat and sodium.[72] The DASH diet has been associated with a reduced risk for HTN, as well as decrease mean blood pressure in those with hypertension.[73-75]

While sodium restriction has been a popular strategy to prevent or treat hypertensive disorders, research on sodium intake during pregnancy and the effects on

blood pressure has long been conflicting.[76] Similarly, a low-sodium diet during pregnancy has not consistently been significantly associated with a decrease in risk for maternal HTN, nor is it recommended to limit intake during pregnancy.[77] In the 1960's, for example, there was research to support that an increase in sodium intake to as much as 10 grams per day may be used to reduce blood pressure in pre-eclamptic patients.[78] Later, in the 1990s, sodium intake was not associated with maternal BP, but was associated with significantly reduced intakes of energy, protein, carbohydrates, fat, Ca, Zn, Mg, Fe and cholesterol.[79] More recently, a clinical study in Southeast Asia found that increased salinity of drinking water was associated with increased maternal blood pressure.[80] On the other hand, a study by Inoue et al. (2016),[81] found no significant associations between urinary salt excretion and maternal BP in Japan.

Current research is also exploring the relationship between sodium and potassium (K), and the ratio that may be most effective for BP reduction.[82] Potassium is an electrolyte that may influence sodium retention by signaling the kidneys, hormonal activation and influence the function of vascular smooth muscle.[83] An analysis of NHANES data determined that higher sodium and lower potassium was associated with increased SBP in non-pregnant persons.[84] In a study by Yilmaz et al. (2017),[85] pregnant women with pre-eclampsia in a low Na/K group had significantly lower mean SBP and DBP (mmHg) levels (148.2 ± 8.9, 92.3 ± 6.2) compared to the mean of the medium Na/K group (155.0 ± 9.1, 97.1 ± 9.5) or high Na/K (158.5 ± 12.2, 99.2 ± 8.57) group; ($p=0.024$, $p=0.0002$, respectively). While these studies do support a significant association between a low Na/K ratio, further research is needed to determine the relationship with BP in healthy, pregnant populations.

In summary, the effect of sodium restriction to decrease maternal BP and to prevent or treat hypertensive disorders during pregnancy is unclear. Further research is needed on the mechanisms by which sodium impacts blood pressure, specifically during pregnancy, as well as the impact of Potassium and various Na/K ratios.

Additional Nutrient Supplementation

Additional nutrients with limited research on their relationship with maternal HTN include essential fatty acids (EFAs), folate, magnesium, antioxidants (specifically vitamins E, C, and selenium), and zinc.

EFAs - Increased essential fatty acids are associated with a greater gestational age and fewer preterm births.[86-89] There is also emerging evidence that essential fatty acids play a role in decreasing placental dysfunction and inflammation and support fetal growth and neurological development. Although EFAs have been associated in animal studies with reduced the risk of maternal HTN and inflammatory markers possibly involved in the pathogenesis, research in human populations is limited.[90,91] Larger intervention studies in women have not found significant associations between EFA supplementation or intake and maternal HTN.[92,93]

Folate – Homocysteine is an amino acid that is associated with cardiovascular disease,[94] and has been associated with the risk for PE and vasoconstriction during pregnancy. It may also increase inflammation and contribute to endothelial dysfunction. Decreased folate concentrations may lead to elevated homocysteine levels, thereby resulting in maternal HTN. In non-pregnant women with folate deficiency, serum folate was inversely related to blood pressure.[95] However, larger meta-analysis have highlighted the conflicting outcomes of the research, and

ultimately determined no difference in maternal risk for hypertensive disorders of pregnancy as a result of folate levels.[96]

Magnesium - Although magnesium intake has been associated with reduced instances of PE, in a double-blind interventional study with ~200 pregnant women, magnesium supplementation was not significantly associated with maternal blood pressure.[97] This is consistent with systematic reviews concluding that there is insufficient evidence to recommend maternal magnesium supplementation to prevent maternal HTN.[98] The underlying mechanism for how magnesium may influence maternal blood pressure, also remains unclear.

Antioxidants - Antioxidants have been associated with endothelial dysfunction, which has been suggested as a mechanism for maternal HTN. However, studies of the supplementation of vitamins C or E or selenium, have found weak or insignificant association with decreasing risk for PE or hypertensive disorders of pregnancy.[99-102]

Zinc - While increased zinc has been associated with decreased oxidation,[103] it is not recommended during pregnancy as a strategy to decrease the risk for maternal high blood pressure. Much of the research related to zinc and maternal blood pressure is inconclusive and largely conflicting.[104]

Dietary Patterns

There is limited research related to overall dietary patterns during pregnancy and maternal BP. One well-known dietary pattern is the Mediterranean diet, which emphasizes whole grains, plant-based foods such as fruits and vegetables, as well as the incorporation of olive oil and fish.[105] The Mediterranean diet has been associated with decreased risk for HTN and cardiovascular disease in the general population,[106]

although low adherence to a Mediterranean-style dietary pattern was not significantly associated with PE or gestation hypertension in an observational study with 3,187 pregnant women.[107] In addition, diet quality as assessed in Project Viva's Alternate Healthy Eating Index, was not associated with the risk for PE.[108] However, in a study with nearly 30,000 Norwegian, pregnant women,[109] dietary patterns emphasizing vegetables, plant foods and vegetable oils were associated with a decreased risk for PE. In the same study, an increased risk for PE was found in dietary patterns emphasizing processed meat, salty snacks, and sweet drinks.

Maternal Blood Pressure and Newborn Birth Weight

A birth outcome that may result from maternal HTN is an infant born with a low birth weight (LBW). Regardless of whether the infant was born at term (~37 weeks gestation) or preterm, LBW is defined as newborn weight < 2500 grams (~5.5lbs). In 2014, the World Health Organization (WHO) reported that nearly 15% newborns worldwide are born with LBW.[110] While some of the known risk factors for LBW are non-modifiable, such as maternal age and ethnicity,[111] modifiable risk factors include infections, drug use, anemia, low maternal BMI and chronic maternal undernutrition.[111,112] Among other things, an infant born with LBW has increased risk for coronary heart disease,[113] impaired cognitive function,[114] and non-insulin dependent diabetes.[115] As a result, in 2016, WHO set a goal of a 30% reduction in newborns with LBW by the year 2025.[116]

The prevalence of low-birth weight in Sub-Saharan Africa, an area including Ghana, is about 13%.[110] To determine risk factors related to LBW in Ghana, a retrospective cohort study with 6,900 participants by Kayode et al. (2014),[117] was

conducted, while controlling for the context of the community in which the mothers resided. Living in a rural setting increased the risk of LBW (OR 1.43, 95% CI: 1.01–2.01; $p < 0.05$), as well as living in a community with a high poverty level (OR 2.16, 95% CI: 1.29–3.61; $p < 0.01$). However, access to community health care services was not significantly associated with the risk of LBW (OR 1.28, 95% CI: 0.87–1.87; $p > 0.05$).

The Generation R study is a population-based prospective cohort study, conducted in the Netherlands with > 8,800 pregnant women.[118] In an analysis of the associations between blood pressure, fetal growth risk, and the risk of adverse birth outcomes, a change in SBP from the second trimester to third trimester was significantly associated with an increased risk for LBW (OR 1.25, 95% CI: 1.12 - 1.40). Furthermore, a change in DBP from the second to third increased the risk (OR 1.49, 95% CI: 1.34 – 1.67), as well as a change between the first and third trimester. This study also found that women with gestational hypertension gave birth to infants with lower birth weights (β = -89 grams, 95% CI: -137 to - 41, $p < 0.01$, respectively), and odds of LBW at 1.85 (95% CI: 1.15 – 2.97) compared to women with normal blood pressure during pregnancy.

Maternal HTN has been associated with an increased risk for adverse birth outcomes primarily in high-income populations. Aside from LBW, outcomes of maternal HTN include increased risk of preterm,[118-120] an infant born small for gestational (SGA),[120,121] with a small head circumference,[118] or still birth.[119,121] While the underlying mechanisms for how maternal BP contributes to birth outcomes remains unclear, mechanisms may involve maternal HTN leading to placental

dysfunction, specifically reduced placental perfusion, and inflammation. Inflammation may lead to fetal hypoxia that may inhibit fetal growth, as well as reduce gestational age, and other pregnancy complications.[86,122,123] Alternatively, one hypothesis is that maternal HTN is actually a consequence of fetal growth restriction. This is based on the idea that to compensate for reduced placental perfusion and decreased birth weight, maternal blood pressure increases.[124]

Conclusion

As a whole, the etiology and underlying mechanisms of maternal high blood pressure are not well understood, further complicated by the nature of individual hypertensive disorders of pregnancy. To avoid risks associated with hypertensive medication, nutrient supplementation to manage maternal blood pressure is of increasing interest. However, research related to the effect of nutrient supplementation or dietary patterns on maternal blood pressure is conflicting. Limitations to current research include inconsistencies in the definitions and specifications of hypertensive disorders, as well as the trimester and duration in which the supplement was being administered. Furthermore, future research is needed to determine the most effective dosages and underlying mechanisms of nutrient supplements to influence blood pressure; specifically, for calcium, vitamin D, and sodium. Maternal blood pressure is also associated with adverse birth outcomes, such as an infant born with a low birth weight, which is associated with long-term chronic disease. Future research is needed to elucidate the pathology of low birth weight caused by maternal high blood pressure. In conclusion, maternal high blood pressure is a major challenge to public health worldwide, and even more-so in developing countries.

CHAPTER 3

EXTENDED METHODOLOGY

Study Setting

The iLiNS study was conducted in southern Ghana, in an area north of Accra, within various semi-urban communities. These communities are primarily subsistence farmers or petty traders, with access to electricity and a public supply of water. Ghana is considered to be a low-middle income country, and residents of these specific communities are not poor or rich by Ghanaian standards. Staple foods included in the regular diet include maize, cassava, rice, fish, and leafy vegetables.

Study Design

This is a secondary data analysis of the International Lipid-Based Nutrient Supplements (iLiNS) Project. iLiNS is a partially double-blind, parallel, randomized controlled trial. The research team recruited pregnant women attending select prenatal clinics, to determine the effects of nutrient supplements during pregnancy and the first eighteen months of the newborn's early childhood. For this analysis, data collected from early pregnancy through birth will be used. A prenatal lipid-based nutrient supplement (LNS) is a paste designed to be mixed with local food to increase the nutrient and energy content for enrolled Ghanaian women during pregnancy and lactation. Multiple micronutrients (MMN) and LNS supplements followed formulations for United Nations Micronutrient Preparation (UNIMAP) previously used in pilot programs among pregnant women.[125] Nutriset S.A.S. (Malaunay, France) produced the LNS in 20g sachets and Dutch State Mines (DSM) South Africa

(Kaiseraugst, Switzerland) produced the capsules of the iron and folic acid (IFA) and MMN supplements. A more detailed description of the study population and methods have previously been described.[126]

The iLiNS study protocol was approved by the institutional review boards at the University of California, Davis; the Noguchi Memorial Institute for Medical Research, University of Ghana; and the Ghana Health Service.

Participants

Eligibility for this study was specific to women attending prenatal clinics, and recruited between December 2009 through December 2011, an age of at least 18 years old, and a gestational age of ≤ 20 weeks. Reasons for exclusion included a test result that was HIV positive at baseline, a gestational age > 20 weeks, residence > 20 km outside of southern Ghana, history of peanut or milk allergies, severe illness, or the intention to move within two years. Participants consented to screen for eligibility, and if eligible, fieldworkers collected anthropometrics and baseline lab values.

Randomization and Blinding

A randomization scheme was designed by a study statistician. Each woman was randomized into either the IFA, MMN, or LNS group. The major steps of the randomization process are as follows:

- Computer-generation (SAS version 9.3) randomized women after baseline assessments into one of three groups.
- A total of 1,320 envelopes (one for each participant), were divided into three groups, and organized into blocks of nine. A block of nine envelopes contained three envelopes for IFA, three for MMN, and three for LNS.

- A nurse shuffled one block of nine envelopes, and the participant chose one envelope to determine group allocation.

To ensure blinding, an independent party from the research team color-coded supplement capsules of the IFA and MMN groups to blind investigators, fieldworkers, and participants. This allowed for sole identification of the capsule to be by color and not supplement content. During follow-up visits, fieldworkers received the color-coded supplement allocations for the participants from the field supervisor. Since LNS was not a capsule, fieldworkers and participants could not be blinded from distinguishing between LNS and IFA or MMN. Fieldworkers were not aware of the group allocations, and data analysts were blinded until the completion of preliminary analyses.

Procedures

At enrollment, the research group distributed surveys to participants and collected demographic characteristics and lab data. The research group collected lab data again at 36 weeks gestation and newborn anthropometric measurements at delivery.

At enrollment, fieldworkers distributed a two week supply of the assigned supplement along with instructions on consumption methods. At bi-weekly, in-home follow-ups with each participant, data on supplement adherence and morbidity, as well as any remaining supplement were collected. Fieldworkers visited the home or hospital at delivery to collect anthropometric measurements of newborns. For 91% of infants, measurements were recorded within 48hrs of birth. Measurements for 9% of

infants were not available after 48hrs, and so measurements were collected between 3-14 days after birth.

Primary Outcomes and Definitions

Our primary outcomes to determine the effect of a nutrition supplement on maternal hypertension are mean SBP and mean DBP at enrollment and 36 weeks gestation. Our primary outcome to determine the association between maternal HTN and birth weight is mean newborn birth weight. High SBP was defined as ≥130 mmHg and high DBP as ≥80 mmHg. Consistent with the iLiNS study, for age- and sex-standardization of blood pressure and weight, the WHO 2006 multi-center growth standard was used.[127] If the baby was measured within 48 hours, birth weight is reported in grams. If after 48 hours, adjustments for weight following the main iLiNS study were employed.

Statistical Analysis - Effect of LNS on Maternal HTN

In this randomized study design, quantifying the as-treated effect of LNS on maternal hypertension was of primary interest. During the study, IFA and MMN capsules were unintentionally mislabeled, causing 92 participants in the IFA group and 85 participants in the MMN group to receive the incorrect supplement. Therefore, this analysis used the supplement treatment assignment actually received and not the treatment originally assigned. A total of 86 women not-exposed in the LNS group, as well as the mixed-exposure women in the IFA or MMN groups were excluded.

The main iLiNS trail included a total sample size of 1,057 (excluding women pregnant during mixed exposure), where IFA = 349, MMN = 354, and LNS = 354.

Our sample size for each group is consistent with the main iLiNS trial and included the total sample size of 1,057. All tests were two-sided, at a 5% level of significance.

Residuals were assessed for normality using a Shapiro-Wilk statistic. Pre-pregnancy body mass index (BMI), C-reactive protein (CRP) at enrollment and α1-acid glycoprotein (AGP) at enrollment were not normally distributed and were logarithmically transformed for analysis. The heteroscedasticity assumption was also examined through the plots and no outliers were identified through visual identification in histograms or scatterplots.

Variables that were possible confounders and had a statistically significant association with the outcome ($p<0.1$ in univariate models) were included in an adjusted regression model. The following potential confounders were considered: pre-pregnancy BMI, gestational age, maternal age, maternal education, assets index, food insecurity score, hemoglobin, parity, history of hypertension, maternal height, CRP, AGP, a positive malaria test, season at maternal enrollment (dry vs wet), marital status, and offspring sex reported at birth.

To avoid collinearity, variables were considered in the separate logistic regression models to assess the effect of the intervention on maternal blood pressure. If a variable was significantly associated with the effect of the intervention, logistic regression was used to determine if the effect of LNS on blood pressure was significantly different between groups. The null-hypothesis was rejected at the 0.05 level.

Linear regression was used to estimate the study intervention effects on blood pressure. For the continuous outcomes, the difference between the three group means

was tested with ANOVA and ANCOVA models. If the null-hypothesis was rejected at the 0.05 level, post-hoc pairwise comparisons across the three intervention groups was tested using the Benjamini-Hochberg procedure to adjust for multiple comparisons.[128]

Due to the number of participants exposed to the incorrect supplement, a sensitivity analysis was conducted to determine if the exclusion of those women influenced the results. The analyses determining the effect of LNS on maternal HTN was repeated with all participants included.

Statistical Analysis - Association between maternal blood pressure and birth weight

We evaluated normality of the residuals using a Shapiro-Wilk statistic. The distributions of pre-pregnancy BMI, CRP and AGP at enrollment had deviations from normality, and were logarithmically transformed for analysis. The heteroscedasticity assumption was examined through the residual versus fit plot. A scatterplot between the independent and dependent variables was visually examined to check that the relationship between the predictor and response was linear. No outliers were visually identified through histograms or scatterplots.

The covariates recorded at enrollment that had a statistically significant association with the outcome ($p<0.1$) were included in adjusted regression models. The covariates recorded at enrollment that were considered for inclusion in an adjusted model are as follows: Pre-pregnancy BMI, gestational age, maternal age, maternal education, assets index, food insecurity score, parity, season at maternal enrollment (dry vs wet), hemoglobin, marital status, history of hypertension, offspring sex, maternal height, CRP, AGP, positive Malaria test, and treatment group.

For continuous predictors, collinearity was checked by running models with covariates and an examination of variance inflation factors (VIF). VIF above 10 was considered problematic, however, there were no variables that exceeded a VIF of two. Therefore, there was no evidence of collinearity and all variables significantly associated with the outcome were included in adjusted models.

Continuous variables were analyzed with linear regression if they were determined to have a statistically significant association with the outcome. Multiple linear regression models were used to determine the association between systolic and diastolic blood pressure and birth weight.

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